

Serial No.: 09/641,802

Confirmation No.: 5387

Filed: August 17, 2000

For: USE OF COLOSTRININ, CONSTITUENT PEPTIDES THEREOF, AND ANALOGS THEREOF TO PROMOTE NEURONAL CELL DIFFERENTIATION

Remarks

The Office Action mailed March 21, 2003 has been received and reviewed.

Claims 16 and 17 having been added, the pending claims are claims 1-17. Reconsideration and withdrawal of the rejections are respectfully requested.

Examiner Interview

A telephonic Examiner's Interview was held on May 20, 2003 between the Applicants' representatives, Supervisory Patent Examiner Kunz and Patent Examiner Nichols, in which the outstanding restriction requirement was discussed. In particular, linking claims 1-6, 9-11, 14, and 15 were discussed. Examiners Kunz and Nichols are thanked for the courtesy of this telephonic interview.

Traverse of the Restriction Requirement

In response to the Restriction Requirement mailed June 18, 2002, Applicants elected, with traverse, Group 37 (claims 1-15), in part drawn to methods of contacting cells *in vivo* with SEQ ID NO:2 (Response to Restriction Requirement, filed July 16, 2002). Applicants continue to traverse this Restriction Requirement, noting that claims 1-6, 9-11, 14 and 15 are linking claims. Accordingly, the Examiner's restriction appears to be more appropriately an election of species with respect to specific sequences. See MPEP 809.02. Thus, Applicants traverse on the grounds that the generic (linking) claims 1-6, 9-11, 14, and 15 include sufficiently few species that a search and examination of all the species at one time would not impose a serious burden on the Examiner. Applicants also request rejoinder and that the requirement be withdrawn upon the finding of an allowable genus.

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Finally, Applicants repeat the request that the Examiner rejoin at least Group 70 (claim 1-15), in part drawn to methods of contacting cells *in vivo* with a specific combination of peptides, to the extent that such combinations include SEQ ID NO:2.

Objection to the Claims

The Examiner objected to claims 1-15 for the recitation of the non-elected inventions SEQ ID NO's 2-34. In view of the Applicants' request for the rejoinder of SEQ ID NO:2-34, discussed above, Applicants respectfully submit that this objection to the claims is moot. Withdrawal of this objection is respectfully requested.

The 35 U.S.C. §112, First Paragraph, Rejection

The Examiner rejected claims 1-15 under 35 U.S.C. §112, first paragraph, because the specification does not reasonably provide enablement for the claimed methods. This rejection of claims 1-15 is respectfully traversed.

First, in rejecting claims 1-8, the Examiner asserted that the specification, while being enabling for promoting neuronal cell differentiation comprising contacting a genus of cells represented by PC12 and SH-SY5Y *in vitro* with SEQ ID NO: 2 or full-length colostrinin, does not reasonably provide enablement for the claimed methods for promoting neuronal differentiation in all cells. This rejection of claims 1-8 is respectfully traversed.

Applicants respectfully disagree. Applicants submit that the PC12 and SH-SY5Y cells lines are well characterized and well accepted models systems for other cell types. And, Applicants submit that the PC12 and SH-SY5Y cells lines are well characterized and well accepted *in vitro* model systems for the study of neuronal differentiation. In support of this statement, Applicants provide the following representative sampling of the scientific literature:

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"[T]he rat pheochromocytoma cell line PC12 has proved to be a very good model system for studying the mechanisms and regulations of neuronal differentiation" (see page 11650, column 2 of Doye et al., *Journal of Biological Chemistry* 15 July 1990;265(20): 11650-11655).

"As well as being an important model for studying neuronal development and the mechanism of action of certain growth factors, this [the PC12 pheochromocytoma cell] system has become useful for the study of the signaling pathways that commit cells to undergo differentiation" (see page 5401, column 2, Altin et al., *Journal of Biological Chemistry*, 25 March 1991;266(9): 5401-5406).

"[T]he rat PC-12 pheochromocytoma cell line is a homogenous model system that has been extensively characterized biochemically and physiologically and shown to be very useful in the study of the differentiation of peripheral sympathetic and sensory neurons" (page 1229, column 1, Cui et al., *Journal of Pharmacology and Experimental Therapeutics*, 1997;280(3): 1228-1234).

"[T]he well characterized neuronal differentiation model PC12" (page 1406, column 1, Lachyankar et al., *Journal of Neuroscience*, 15 February 2000;20(4):1404-1413).

"The rat pheochromocytoma cell line PC12 is extensively used as a model of neuronal cell differentiation" (abstract, page 29153, Anneren et al., *Journal of Biological Chemistry*, 15 September 2000;275(37): 29153-29161).

"Clonal pheochromocytoma (PC12) cells . . . have become currently a very important model for the study of neuronal differentiation" (page 104, column 1, Xiang-Ming et al., *Acta Pharmacol Sin*, February 2001;22(2): 103-110).

"SH-SY5Y human neuroblastoma cells, which are a well characterized system for studying neuronal growth and differentiation" (page 21268, column 2, Kim et al., *Journal of Biological Chemistry*, 22 August 1997;272(34): 21268-21273).

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"SH-SY5Y human neuroblastoma cells are a well characterized *in vitro* model of nervous system growth" (abstract, page 4881, Kim et al., *Endocrinology*, 1998;139(12): 4881-4889).

"The human SH-SY5Y neuroblastoma cell line is a well established system for studying neuronal differentiation" (page 30341, column 1, Feng and Porter, *Journal of Biological Chemistry*, 22 October 1999;274(43): 30341-30344).

"SH-SY5Y cells . . . undergo morphological and functional neuronal differentiation when exposed to appropriate stimuli and, therefore, are often used as a model for studying neuronal development" (page 124, column 1, Puglianiello et al., *Journal of Endocrinology*, 2000;165: 123-131).

Thus, as demonstrated by the scientific literature, Applicants respectfully submit that the PC12 and SH-SY5Y cell lines are well characterized and well accepted *in vitro* model systems for other cell types and for the study of neuronal differentiation.

In rejecting claims 9-13 under 35 U.S.C. §112, first paragraph, the Examiner asserted that "[w]hile the specification and prior art offers sufficient support to the claims that colostrinin and SEQ ID NO:2 can stimulate cell differentiation in neuronal cells such as PC12 and SHSY5Y *in vitro*, no evidence is provided re: successful stimulation of cell differentiation using SEQ ID NO:2 in animals, [or] successful treatment of human patients wherein cell differentiation was initiated using SEQ ID NO:2. A skilled artisan would have no reasonable expectation of success that administration of colostrinin or SEQ ID NO:2 would act as a 'neuronal cell regulator'" (page 8, paragraph 19, Office Action mailed March 21, 2003 (emphasis in original)).

Applicants respectfully disagree. As discussed above, both the PC12 and SH-SY5Y cell lines are well accepted *in vitro* models system for the study of neuronal cell differentiation. The Examiner has, in essence, required the Applicant to present data from *in vivo* animal experiments or from human clinical trials. This is inappropriate. According to MPEP § 2164.02, an example of an *in vitro* model in the specification, in effect, constitutes a

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"working example" if that example "correlates" with a disclosed or claimed method invention. In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the Examiner has evidence that the model does not correlate. Further, "the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example." The Examiner has provided no such reasons in his Office Action, March 21, 2003.

Further, Applicants submit that the correlation between the *in vitro* model systems provided by the PC12 and SH-SY5Y cells lines and *in vivo* results is well accepted. In support of this statement, Applicants provide the following representative sampling of the scientific literature, supporting the correlation between *in vitro* results with the SH-SY57 and PC12 cells lines and *in vivo* results:

Noble et al., *Molecular Pharmacology*, 2000;58:159-166; Demonstrating the similarity of the stimulation of μ - or δ -opioid receptors both *in vitro* in the SH-SY57 cell line and *in vivo* in different strains of mice and rats.

DeJongh et al., *Toxicology and Applied Pharmacology*, 1999; 158:261-268; Demonstrating acrylamide toxicity both *in vitro* in the SH-SY5Y cell line and *in vivo* in rats.

Chen et al., *Journal of Neurochemistry*, 1998;70(4): 1768-1771; Demonstrating the induction of tyrosine hydroxylase by lithium both *in vitro* in the SH-SY5Y cell line and *in vivo* in the frontal cortex, hippocampus, and striatum of male Wistar rats.

Ponthan et al., *Int. J. Cancer*, 2003;104: 418-424; Demonstrating toxicity and antiproliferative effects of the synthetic retinoid Ro 13-6307 both *in vitro* in SH-SY5Y cells and *in vivo*, in a rat neuroblastoma xenograft model.

Zhen et al., *Psychopharmacology*, 2002;162: 379-384; Demonstrating the stimulation of protein tyrosine phosphatase (PTPase) by lithium both *in vitro* in the PC12 cell line and *in vivo* in rat brains.

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Dago et al., *Journal of Neurochemistry*, 2002;81: 17-24; Demonstrating the correlation of the neuroprotective effect of compound NS1231 *in vitro* in PC12 cells with the neuroprotective effect of compound NS1231 *in vivo* in both a gerbil model of transient global ischaemia and a mouse middle cerebral artery occlusion model.

Bagchi et al., *Toxicology Letters*, 1997;91: 31-37; Demonstrating similar protein kinase C (PKC) stimulatory effects *in vitro*, with the PC12 cell line, and *in vivo*, with Sprague-Dawley rats, by the administration of various pesticides and transition metal salts, all known to induce oxidative stress.

In view of the above discussion, Applicants respectfully submit that the specification provides adequate instruction and guidance for the methods of claims 9-13, for promoting neuronal cell differentiation in a patient.

Finally, in rejecting claims 14 and 15 under 35 U.S.C. §112, first paragraph, the Examiner asserted "[w]hile the specification and prior art offers sufficient support to the claims that colostrinin and its active peptide analog SEQ ID NO:2 can stimulate cell differentiation in neuronal cell lines such as PC12 and SHSY5Y *in vitro* no evidence is provided re: successful conversion of damaged cells into function (*sic*) cells using SEQ ID NO:2, successful treatment of human patients wherein revival was initiated using SEQ ID NO:2. Thus, the skilled artisan lacks the guidance necessary to practice the claimed invention of claims 14 and 15 with a reasonable expectation of success" (pages 12-13 of Office Action mailed March 21, 2003.)

Applicants respectfully disagree. Again, the Examiner has, in essence, required the Applicant to present data from *in vivo* animal experiments or from human clinical trials. This is inappropriate (see MPEP § 2164.02). And furthermore, Applicants express their confusion with the Examiner's statements of paragraphs 27-29 of the Office Action mailed March 21, 2003. Clarification is requested.

To the extent that the Applicants understand the Examiner's statements the following argument is presented. In paragraph 27, the Examiner states Janusz et al. (WO 98/14773, pp. 20-21) "does not teach that colostrinin has the effect of a '*neuronal cell regulator*'"

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(emphasis in original)). In paragraph 28, the Examiner discusses various aspects of products of product-by-process claims. Then, in paragraph 29, the Examiner concludes "[t]hus colostrinin, PRP, and NP peptides disclosed by WO 98/144773, being active analogs of SEQ ID NO:2, do not have the '*neuronal cell regulator activity*' as claimed by the instant application (emphasis in original)." This is an inappropriate conclusion. Indeed, Applicants submit that Janusz et al. provide no teaching that colostrinin has the effect of a neuronal cell regulator. However, it is inappropriate to conclude from this silence that colostrinin, its constituent peptides and analogs thereof will *not* have activity as neuronal cell regulators.

Further, the Examiner asserted that the prior art teaches that colostrinin and select peptide fragments thereof "have activity as cytokines and not as neuronal cell regulators" (page 13, paragraph 32 of Office Action mailed March 21, 2003). The Examiner then asserted that PRP, a colostrinin constituent peptide, "is useful for treating autoimmune disease, not neurodegeneration or any nervous system nonfunction Thus the prior art gives the skilled artisan support for the use of colostrinin and SEQ ID NO:2 for the treatment of immune cell nonfunction not neuronal cell nonfunction" (pages 13-14, paragraph 33 of Office Action mailed March 21, 2003). Applicant's respectfully disagree. The teachings of the effect of colostrinin for the treatment of immune cell nonfunction and the claimed methods of treating damaged neuronal cells are not mutually exclusive. Applicants respectfully submit that the specification provides adequate instruction and guidance for the methods of claims 14 and 15.

In view of the arguments presented above, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-15 under 35 U.S.C. §112, first paragraph.

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Summary

It is respectfully submitted that the pending claims 1-17 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for
The Board of Regents, University of Texas System

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July 18, 2003
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CERTIFICATE UNDER 37 CFR §1.10:

"Express Mail" mailing label number: **EVO 7373 5232 43** Date of Deposit: July **18**, 2003

The undersigned hereby certifies that this paper is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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**JUL 18 2003 APPENDIX A - SPECIFICATION/CLAIM AMENDMENTS
INCLUDING NOTATIONS TO INDICATE CHANGES MADE**

**Serial No.: 09/641,802
Docket No.: 265.00240101**

Amendments to the following are indicated by underlining what has been added and bracketeting what has been deleted.

In the Claims

For convenience, all pending claims are shown below.

1. A method for promoting cell differentiation, the method comprising contacting cells with a neuronal cell regulator selected from the group of colostrinin, a constituent peptide thereof, an active analog thereof, and combinations thereof, under conditions effective to change the cells in morphology to form neuronal cells; wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to one or more constituent peptides of colostrinin, which are selected from the group of SEQ ID NO:1 through SEQ ID NO:34.
2. The method of claim 1 wherein the cells are present in a cell culture, an organ, a tissue, or an organism.
3. The method of claim 1 wherein the cells are mammalian cells.
4. The method of claim 3 wherein the cells are human cells.
5. The method of claim 1 wherein the cells are pluripotent cells.
6. The method of claim 1 wherein the neuronal cell regulator is a constituent peptide of colostrinin.

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7. The method of claim 6 wherein the neuronal cell regulator is selected from the group of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFF LPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFVF (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQ P (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPP PQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQ NILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGFPILV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), VESYVPLFP (SEQ ID NO:31), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), and combinations thereof.

8. The method of claim 7 wherein the neuronal cell regulator is selected from the group of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFF LPVVNVLP (SEQ ID NO:4), DLEMPVLPVEPFVF (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), and combinations thereof.

9. A method for promoting neuronal cell differentiation in a patient, the method comprising administering to the patient a neuronal cell regulator selected from the group of colostrinin, a constituent peptide thereof, an active analog thereof, and combinations thereof, under conditions effective to promote differentiation of cells to form neuronal cells; wherein the active analog

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comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to one or more constituent peptides of colostrinin, which are selected from the group of SEQ ID NO:1 through SEQ ID NO:34.

10. The method of claim 9 wherein the patient is a human.

11. The method of claim 9 wherein the neuronal cell regulator is a constituent peptide of colostrinin.

12. The method of claim 11 wherein the neuronal cell regulator is selected from the group of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2), DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFPLPVNVLP (SEQ ID NO:4), DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6), VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), VVMEV (SEQ ID NO:9), SEQP (SEQ ID NO:10), DKE (SEQ ID NO:11), FPPPK (SEQ ID NO:12), DSQPPV (SEQ ID NO:13), DPPPQS (SEQ ID NO:14), SEEMP (SEQ ID NO:15), KYKLQPE (SEQ ID NO:16), VLPPNVG (SEQ ID NO:17), VYPFTGPIPN (SEQ ID NO:18), SLPQNILPL (SEQ ID NO:19), TQTPVVVPPF (SEQ ID NO:20), LQPEIMGVPKVKETMVPK (SEQ ID NO:21), HKEMPFPKYPVEPFTESQ (SEQ ID NO:22), SLTLTDVEKLHLPLPLVQ (SEQ ID NO:23), SWMHQPP (SEQ ID NO:24), QPLPPTVMFP (SEQ ID NO:25), PQSVLS (SEQ ID NO:26), LSQPKVLPVPQKAVPQRDMPIQ (SEQ ID NO:27), AFLLYQE (SEQ ID NO:28), RGPFPLV (SEQ ID NO:29), ATFNRYQDDHGEEILKSL (SEQ ID NO:30), VESYVPLFP (SEQ ID NO:31), FLLYQEPVLGPVR (SEQ ID NO:32), LNF (SEQ ID NO:33), and MHQPPQPLPPTVMFP (SEQ ID NO:34), and combinations thereof.

13. The method of claim 12 wherein the neuronal cell regulator is selected from the group of MQPPPLP (SEQ ID NO:1), LQTPQPLLQVMMEPQGD (SEQ ID NO:2),

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DQPPDVEKPDLQPFQVQS (SEQ ID NO:3), LFFFPLPVNVLP (SEQ ID NO:4),
DLEMPVLPVEPFPFV (SEQ ID NO:5), MPQNFYKLPQM (SEQ ID NO:6),
VLEMKFPPPPQETVT (SEQ ID NO:7), LKPFPKLKVEVFPFP (SEQ ID NO:8), and
combinations thereof.

14. A method for treating damaged neuronal cells, the method comprising contacting nonfunctional neuronal cells with a neuronal cell regulator selected from the group of colostrinin, a constituent peptide thereof, an active analog thereof, and combinations thereof, under conditions effective to convert the damaged neuronal cells to functional neuronal cells; wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to one or more constituent peptides of colostrinin, which are selected from the group of SEQ ID NO:1 through SEQ ID NO:34, and wherein the nonfunction is the result of neurodegeneration.

15. A method for treating damaged neuronal cells in a patient, the method comprising administering to the patient a neuronal cell regulator selected from the group of colostrinin, a constituent peptide thereof, an active analog thereof, and combinations thereof, under conditions effective to convert damaged neuronal cells to functional neuronal cells; wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to one or more constituent peptides of colostrinin, which are selected from the group of SEQ ID NO:1 through SEQ ID NO:34 and wherein the nonfunction is the result of neurodegeneration.

16. [New] A method for promoting neuronal cell differentiation, the method comprising contacting pluripotent cells of the nervous system with a neuronal cell regulator selected from the group of colostrinin, a constituent peptide thereof, an active analog thereof, and combinations thereof, under conditions effective to change the pluripotent cells of the nervous

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system in morphology to form neuronal cells; wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to one or more constituent peptides of colostrinin, which are selected from the group of SEQ ID NO:1 through SEQ ID NO:34.

17. [New] A method for promoting neuronal cell differentiation in a patient, the method comprising administering to the patient a neuronal cell regulator selected from the group of colostrinin, a constituent peptide thereof, an active analog thereof, and combinations thereof, under conditions effective to promote differentiation of pluripotent cells of the nervous system to form neuronal cells; wherein the active analog comprises a peptide having an amino acid sequence with at least about 15 percent proline and having at least about 70 percent structural similarity to one or more constituent peptides of colostrinin, which are selected from the group of SEQ ID NO:1 through SEQ ID NO:34.
